

Immunization update and hot topics in clinical immunology: How does this relate to my practice?

Joseph A. Bellanti, M.D.

ABSTRACT

The prevention of infectious diseases by the use of vaccines represents one of medicine's greatest triumphs during the 20th century. This era has witnessed the global eradication of smallpox as a result of Jennerian cowpox vaccination, the elimination of paralytic poliomyelitis from the western hemisphere, and within 5–10 years the anticipated eradication of poliomyelitis worldwide as a result of the poliovirus vaccines. Next slated for worldwide eradication is measles, the great killer of infants and children, which each year extracts a global mortality of one million victims. Throughout the 20th century the percutaneous (i.e., subcutaneous or intramuscular) route has almost exclusively been the preferred way to administer vaccines. However, as a result of several important scientific discoveries made during the 20th century, including new tissue-culturing techniques, the development of recombinant DNA technology, and genetic sequencing, a whole new generation of tailor-made modern vaccines has become available, including DNA vaccines and transgenic plant vaccines. Moreover, it became apparent that alternative routes of administration of vaccines, such as by aerosol immunization might be more appropriate and more effective than immunization via the parenteral route. The overall success in vaccine development, however, has not been without cost. For every new vaccine that has been developed, an adverse effect has been seen. Thus, although modern vaccines are extremely safe and effective, they are neither completely safe nor completely effective. The goal of vaccine development, therefore, is to achieve the highest degree of protection and the lowest rate of adverse effects. This paper describes some of the recent advances in vaccine development and will focus on some hot topics relating to the recent development and use of respiratory aerosolized vaccines.

(Allergy Asthma Proc 27:456–464, 2006; doi: 10.2500/aap.2006.27.2896)

Never in the history of human progress has a better and cheaper method of preventing illness been developed than immunization at its best

Edsall

The prevention of infectious diseases by the use of vaccines represents one of medicine's greatest triumphs during the 20th century.¹ This era has witnessed the global eradication of smallpox as a result of the Jennerian cowpox vaccination, the elimination of paralytic poliomyelitis from the western hemisphere, and within 5–10 years the anticipated eradication of poliomyelitis worldwide as a result of the poliovirus vaccines. Next slated for worldwide eradication is measles, the great killer of infants and children, which each year extracts a global mortality of 1 million victims.² Throughout the 20th century the percutaneous (i.e., subcutaneous or intramuscular) route has almost exclusively been the preferred way to administer vaccines.¹ However, as a result of several important scientific discoveries made during the 20th century,

including new tissue-culturing techniques, the development of recombinant DNA technology, and genetic sequencing, a whole new generation of tailor-made modern vaccines has become available, including DNA vaccines and transgenic plant vaccines. Moreover, it became apparent that alternative routes of administration of vaccines, such as by aerosol immunization, might be more appropriate and more effective than immunization *via* the parenteral route. The overall success in vaccine development, however, has not been without cost; for every new vaccine that has been developed an adverse effect has been seen. Thus, although modern vaccines are extremely safe and effective, they are neither completely safe nor completely effective. Therefore, the goal of vaccine development is to achieve the highest degree of protection and lowest rate of adverse effects. This paper describes some of the recent advances in vaccine development and will focus on some hot topics relating to the recent development and use of respiratory aerosolized vaccines.

WHY DO VACCINES CONTINUE TO BE IMPORTANT IN THE 21st CENTURY?

Table 1 shows several events that have occurred in recent years and continue to lend increasing importance to vaccines as we begin the 21st century. Despite the development and availability of powerful antibiotics, bacteria continue to emerge with resistant properties that are responsible for serious and sometimes fatal

From the Departments of Pediatrics and Microbiology–Immunology and the International Center for Interdisciplinary Studies of Immunology, Georgetown University Medical Center, Washington, D.C.

Address correspondence and reprint requests to Joseph A. Bellanti, M.D., Georgetown University Medical Center, Kober Cogan Building, Room 318, 3800 Reservoir Road, NW, Washington, D.C. 20057

E-mail address: eic1aap@aol.com

Copyright © 2006, OceanSide Publications, Inc., U.S.A.

Table 1 Several recent factors that have stimulated vaccine development

Emergence of antibiotic-resistant bacteria
Appearance of new infectious diseases, <i>e.g.</i> , SARS
Use of microorganisms as vectors of bioterrorism, <i>e.g.</i> , anthrax
New developments in vaccine development and delivery systems, <i>e.g.</i> , nasal influenza vaccine (FluMist)

infections, *e.g.*, staphylococci and pneumococci. Equally important is the emergence of new and virulent diseases for which vaccines are ideally suited for their control, *e.g.*, SARS. Bioterrorism has introduced new biological weapons that have stimulated vaccine development to counter these new threats. Finally, the availability of new delivery systems for the administration of vaccines, *e.g.*, nasal influenza vaccine (FluMist; MedImmune Vaccines, Inc., Gaithersburg, MD), has given new impetus to the development of vaccine regimens with greater efficacy.

WHAT IS THE ROLE OF THE ALLERGIST-IMMUNOLOGIST IN VACCINE USAGE?

The origins of allergy are intertwined with those of infectious diseases and many of the contributions to the field of allergy were made by those individuals who were microbiologists or who were interested primarily in infectious diseases. The basis for this relationship derives from the recognition that recovery from an infectious disease imparted a protection to the host that was defined subsequently as immunity, which then led to attempts at artificially inducing immunity by the inoculation of the host with modified or attenuated infectious disease agents in the form of vaccines. However, the outcome of immunization was recognized quite early by von Pirquet³ not to be always beneficial but could, at times, be associated with harmful adverse reactions. It was within this cradle of beneficial and detrimental consequences of the immune response to infectious diseases that discoveries were made subsequently by Pirquet and several others, which paved the way for the development of the field of allergy.

By the same token, because allergist-immunologists historically and currently possess specialized expertise in the preparation and use of therapeutic inoculation, they hold a pivotal position in medicine in the area of vaccine usage. Moreover, expertise in the area of current vaccine development and use broadens the vistas of the allergist-immunologist and holds the key to resolving the emerging challenges of new disease entities, which are based on immunologic principles. The challenge of emerging new infectious diseases, *e.g.*,

Table 2 Some current and newly developed vaccines

Hepatitis A and hepatitis B vaccines
DTaP vaccine
Polio OPV → IPV
MMR
Varicella
Conjugate vaccines, <i>i.e.</i> , Hib, pneumo
Meningococcal (A, C, Y, and W-135); new conjugate vaccine
New nasally administered vaccines, <i>i.e.</i> , influenza (FluMist) and measles

DTaP = diphtheria, tetanus, and acellular pertussis vaccine; IPV = inactivated poliovirus vaccine; OPV = oral poliovirus vaccine.

SARS, and the autoimmune manifestations of viral infection, *e.g.*, Epstein-Barr infection, chronic fatigue syndrome, and fibromyalgia, present unique opportunities for the contributions of the allergist-immunologist. The allergist-immunologist can now respond more effectively to these challenges armed with the new knowledge and new products of modern technology, which have been made possible by the many contributions of those who came before us. Finally, the allergist-immunologist is the first to be called in consultation for vaccine adverse effects and the most knowledgeable of adverse effects of vaccines in atopic patients.

CURRENT AND NEWLY DEVELOPED VACCINES

Table 2 shows a listing of some of the current and newly developed vaccines that have become clinically available. These vaccines have been particularly useful in high-risk groups such as infants and elderly people and in patients with underlying chronic cardiac (*e.g.*, congestive heart disease), pulmonary (*e.g.*, asthma), and metabolic diseases (*e.g.*, diabetes). Figure 1 shows the most current recommended immunization schedule for children and adolescents.

MATURATIONAL EFFECTS ON VACCINE RESPONSES

One of the important variables affecting vaccine efficacy is the state of maturation of the immune system. It is now generally recognized that the reactivity of the immunologic system is lowest at both ends of the age spectrum of human subjects. Table 3 shows some of the maturational effects of infancy that affect vaccine efficacy in infancy. Similarly, elderly people have diminished reactivity to vaccines based on a weakened function of organ systems,

Recommended Childhood and Adolescent Immunization Schedule UNITED STATES • 2006

Vaccine ▼	Age ►	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	24 months	4–6 years	11–12 years	13–14 years	15 years	16–18 years
Hepatitis B ¹	HepB		HepB	HepB ¹		HepB						HepB Series			
Diphtheria, Tetanus, Pertussis ²			DTaP	DTaP	DTaP		DTaP			DTaP	Tdap		Tdap		
<i>Haemophilus influenzae</i> type b ³			Hib	Hib	Hib ³	Hib									
Inactivated Poliovirus			IPV	IPV		IPV				IPV					
Measles, Mumps, Rubella ⁴						MMR				MMR		MMR			
Varicella ⁵						Varicella						Varicella			
Meningococcal ⁶												MCV4		MCV4	
Pneumococcal ⁷			PCV	PCV	PCV	PCV				PCV		PPV			
Influenza ⁸						Influenza (Yearly)						Influenza (Yearly)			
Hepatitis A ¹												HepA Series			

Figure 1. Recommended childhood and adolescent immunization schedule. (United States 2006: www.cdc.gov/nip/; last accessed Jan. 5, 2006.)

Table 3 Maturation effects during infancy on vaccine responses

Aspect	Example	Causative Mechanism
Maternal Ab	Inhibitory effect on live attenuated viral vaccines; MMR and varicella vaccines delayed until 1 yr of age	Passive transfer of IgG Ab to the neonate
Immature T-cell function	Deficiency of Ab to polysaccharide vaccines in infants <2 yr, e.g., Hib and pneumococcal vaccines	Th2 skewing (Th2 > Th1)

Ab = antibody.

OceanSide Publications

Table 4 Maturation effects of elderly people on vaccine responses

Aspect	Example	Causative Mechanism
People >60 yr old who have lower serum Ab responses to immunization	Influenza virus vaccine	Reduced capability to mount a "primary" response
Elderly people retain the ability to mount a "secondary" response	Pneumococcal vaccine	Long-lived memory T and B cells

Ab = antibody.

including the immune system. Shown in Table 4 shows some of the maturational effects of elderly people that affect vaccine efficacy.

FUTURE ALTERNATIVE VACCINE STRATEGIES

Table 5 shows some alternative vaccine strategies that have become available as a result of several important scientific discoveries and technological

advances made during the 20th century. These include new tissue-culturing techniques, the development of recombinant DNA technology, and genetic sequencing, a whole new generation of tailor-made modern vaccines including DNA vaccines and transgenic plant vaccines. Coupled with these discoveries have been advances in our understanding of the mucosal-associated lymphoid tissues,⁴ which have

Table 5 Future alternative vaccine strategies

Recombinant DNA vaccines
Conjugated polysaccharides*
Synthetic peptide vaccines
Anti-idiotypic vaccines
Virus-carrier vaccines (vaccinia)
Mucosal vaccines (influenza and measles)*

*In current use.

Table 6 Advantages of aerosol route of immunization

Mucosal immunization stimulates both 'local' (sIgA and CMI) and 'systemic' immunity (IgG and CMI)
A "needle-less" method, ease and efficiency of vaccination to large population by nonmedical staff
Elimination of blood borne transmission of viral agents (*e.g.*, hepatitis and HIV)
Allows immunization of younger infants, *e.g.*, 4–6 months; no inhibitory effect of maternal antibody
A cost-effective, safe, and noninvasive method

CMI = cell-mediated immunity.

provided a basis for new vaccine delivery systems such as aerosol delivery systems for influenza and measles vaccines.⁵

ADVANTAGES OF THE AEROSOL ROUTE OF IMMUNIZATION

There are a number of advantages of the aerosol route of immunization (Table 6). In contrast to parenteral routes of immunization, which stimulate predominantly systemic IgG-associated antibody and cell-mediated immunity responses, mucosal immunization stimulates both mucosal (sIgA and cell-mediated immunity) responses as well as systemic immune responses. The methodology is particularly well-suited as an easily performed, cost-effective method of immunization for developing countries where large numbers of subjects can be immunized in a short period of time. The method obviates the disposal problem and avoids the reuse of disposable needles and syringes with resultant spread of hepatitis and HIV, which are major problems in developing countries. A major advantage of the method is that it allows immunization of younger infants, *e.g.*, 4–6 months of age (the most vulnerable age group), without the inhibitory effects of maternal antibody as seen in the case of vaccines that are administered by the parenteral route.

Table 7 Current status of some aerosolized vaccines: Influenza nasal vaccine (live, attenuated)

Over the past 20 yr, a live attenuated CAIV was developed; administered by nasal spray was approved by the FDA (2003)
Attenuation at 25° C prevents replication of virus vaccine in lung (37° C) stimulating local (sIgA protective antibody) in nasal secretions as well as serum IgG
85–90% protection and reduction of otitis media in children
An ideal candidate for universal immunization

FDA = Food and Drug Administration.

CURRENT STATUS OF SOME AEROSOLIZED VACCINES: INFLUENZA VACCINE (LIVE, ATTENUATED)

Over the past 20 years, a major investigative effort has been directed to the development of a live attenuated cold-adapted influenza vaccine (CAIV-T)⁶ and in 2003 the Food and Drug Administration approved the licensure of the first nasal influenza vaccine (FluMist). The vaccine virus was developed by attenuation at 25°C, which prevents replication of the virus vaccine in lung tissue (37°C), thereby preventing lower respiratory tract infection but allowing sufficient viral replication in the nasopharynx to stimulate specific mucosal and systemic immune responses (Table 7).

In several studies, CAIV-T was found to be safe with no serious adverse effects. Protection was inversely related to age and ranged from 70% for 10- to 18-year-old children to 91% for children <5 years of age. A single dose was sufficient for protection.⁶ The protection was directed not only at the immunizing strains but also showed cross-reactivity with other influenza strains and persisted through two seasons. All of these characteristics support CAIV-T as a good candidate not only for protecting school children and working adults from influenza but also for reducing the spread of influenza in the community. These studies were performed before licensure of CAIV-T and are being extended with the licensed product, FluMist, in the same setting. The CAIV-T is an important addition to our armamentarium against influenza. The advantages of this preparation should be used to the fullest extent possible to reduce the impact of influenza.

CURRENT STATUS OF SOME AEROSOLIZED VACCINES: MEASLES AEROSOL VACCINE

The current status of measles aerosol vaccines is shown in Table 8. Studies of aerosolized measles vaccination, originally launched in Mexico by Sabin *et al.*,^{7,8} have continued and have shown great efficacy

Table 8 Current status of some aerosolized vaccines: Measles aerosol vaccine

Studies of aerosolized measles vaccination were originally launched in Mexico by Sabin *et al.* in 1983^{7,8} continued by others⁹⁻¹⁴

Sabin *et al.*⁷ showed superiority of vaccine grown in human diploid cell line containing the EZ strain over that grown in chick embryo fibroblast containing Schwarz strain

Sabin *et al.*⁷ showed that inhalation of undiluted aerosolized measles vaccine was immunogenic in 100% of 4- to 6-month-old children with or without maternal antibody

Bellanti *et al.*¹⁵ working with Mexican colleagues have compared mucosal and serum antibody responses of Mexican children immunized either by SQ or aerosolized immunization

The results thus far show that the aerosolized immunization *via* the mucosal route has greater effectiveness than immunization *via* the SQ route

SQ = subcutaneous.

not only with measles but also with the rubella and mumps vaccines.⁹⁻¹⁴ In a set of seminal studies Sabin showed several key attributes of aerosol immunization and described its major advantage of its capacity to immunize younger infants without the inhibitory effects of maternal antibody as well as the superiority of vaccine grown in human diploid cell line containing the Edmonston-Zagreb strain over that grown in chick embryo fibroblast containing the Schwarz strain. Bellanti *et al.*¹⁵ have continued these studies in collaboration with Mexican colleagues and have established the superiority of nasal administration of measles vaccine in stimulating both measles-specific mucosal and serum antibody over that seen after subcutaneous administration (Fig. 2).

MEASLES VACCINE AND THE RISK OF AUTISM

Despite the general acceptance of vaccines as the quintessential monument to disease prevention and a remarkable safety record, for a surprising number of vaccines, there have been widely publicized but unsubstantiated claims of adverse effects.¹⁶ Table 9 shows some examples of unsubstantiated claims of adverse vaccine effects. The live attenuated measles virus component in the vaccine against measles, mumps, and rubella (MMR) has been erroneously linked as a cause of autism. The hypothesis derives from research of Wakefield *et al.*¹⁷ involving a small number of young children with chronic gastrointestinal symptoms and behavioral abnormalities. These researchers speculated on a causal relationship

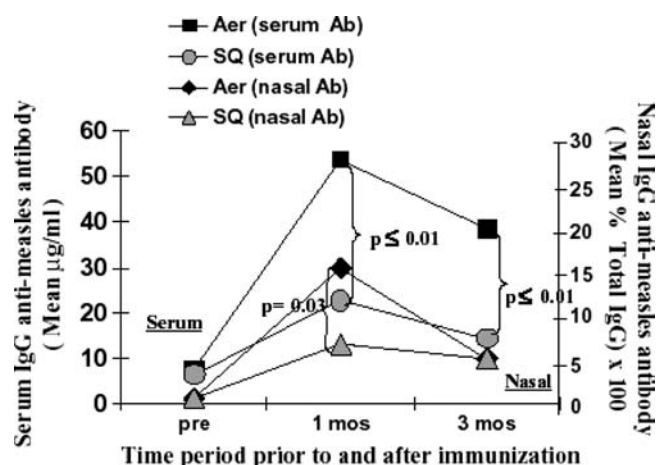


Figure 2. Comparison of specific serum IgG and nasal IgG anti-measles antibody from children before (pre-) and response at 1 and 3 months after booster measles immunization by either subcutaneous (SQ) or aerosol (Aer) route. (Reproduced with permission from Ref. 15.)

among MMR vaccination, abnormalities in lymphoid tissue, and developmental disorders such as autism and the putative identification of the measles viral genome in gastrointestinal biopsy material from these children (which has not been substantiated by other investigators). Collectively, these findings have led these investigators to conclude that the measles virus in the MMR vaccine is a cause of autism in children. A study by Madsen *et al.*¹⁸ provides an objective analysis of the rates of autism in relation to MMR vaccination status in a well-defined population of more than half a million children in Denmark, about one-fifth of whom had not received the MMR vaccine. This careful study did not detect an association between MMR and autism. Unsubstantiated accusations that a vaccine causes harm have had serious and negative consequences not only in eroding public confidence in vaccine usage but also on companies that produce vaccines, which because of negative economic effects, little profit and huge liability have withdrawn effective vaccines from the market. This makes it difficult to run vaccination programs, including those in developing countries where the needs are greatest. Although adverse effects are seen in extremely small numbers, the risk/benefit ratio for vaccine usage is certainly in favor of vaccines.

MENINGOCOCCAL VACCINES

Another hot topic in clinical immunology is the development of new and more effective meningococcal vaccines.¹⁹ The five major pathogenic serogroups of the Gram-negative encapsulated bacterium *Neisseria meningitidis* are A, B, C, Y, and W135. In the 1960s, vaccines consisting of purified capsular polysaccharide

Table 9 Examples of unsubstantiated claims made about some vaccines

Vaccine	Unsubstantiated Adverse Effects
Measles vaccine	Autism and related developmental disorders
DPT vaccine	Sudden infant death syndrome
<i>Haemophilus influenzae</i> type b	Diabetes mellitus
Inactivated polio vaccine	Paralytic poliomyelitis; SV40 infection
Hepatitis B vaccine	Multiple sclerosis
Anthrax vaccine	Fatigue; Gulf War syndrome
Lyme disease vaccine	Chronic inflammatory arthritis
"Hot lots" (some batches of any vaccine)	Multiple systemic problems
Multiple vaccinations	Undefined harmful immunologic effects from vaccine interactions

Source: Ref. 16 (reproduced with permission).

DPT = diphtheria, pertussis tetanus vaccine.

antigens were developed against serogroups A, C, Y, and W135. Although polysaccharide vaccines are safe and highly immunogenic in older children and adults, they were not efficacious among infants and young children <2 years of age. Capsular polysaccharide-protein conjugate vaccines were subsequently developed. Monovalent serogroup C conjugate vaccines have been successful in reducing the burden of serogroup C meningococcal disease among infants, older children, and adults in the United Kingdom and Canada. Tetravalent serogroup A/C/W/Y conjugate vaccines recently have been licensed. Group B polysaccharide is poorly immunogenic, even when conjugated to a protein carrier. This has been attributed to the similarity of the group B polysaccharide to cell membrane antigens of the human subjects. The use of serogroup B capsular polysaccharide as the basis for a vaccine for prevention of serogroup B meningococcal disease therefore has proved problematic. One new approach to solving this dilemma has been made possible by the recent sequencing of the serogroup B genome, which has led to the identification of additional, genome-derived, neisserial antigens, through a process called "reverse vaccinology."²⁰⁻²²

ISSUES SURROUNDING AEROSOL VACCINES

Inactivated Intranasal Influenza Vaccine and the Risk of Bell's Palsy

As described previously, although modern vaccines are extremely safe and effective, they are sometimes associated with unexpected adverse effects. In a recent study by Mutsch *et al.*,²³ an unusual increased risk of Bell's palsy was observed in recipients of an inactivated virosomal-subunit influenza vaccine licensed in Switzerland (Nasalflu; Berna Biotech, Bern, Switzerland) containing an *Escherichia coli* heat-labile toxin as a mucosal adjuvant. The relative risk of Bell's palsy was estimated to be 19 times the

risk in the controls, corresponding to 13 excess cases per 10,000 vaccinees within 1-91 days after vaccination. In contrast, there was essentially no risk of Bell's palsy after receipt of the traditional, parenteral influenza vaccine.

Two questions emerge from this study:

1. Is there cause for concern about the use of the current inactivated influenza vaccines given parenterally? The complication of Bell's palsy in this study appeared to be related to the presence of the *E. coli* heat-labile toxin mucosal adjuvant, which led to an unexpected autoimmune reaction. The results of the study indicate clearly that the parenteral use of the standard inactivated influenza vaccine (which does not contain the *E. coli* heat-labile toxin adjuvant) did not confer an increased risk of Bell's palsy. Thus, the current public health procedure of administering inactivated influenza vaccine parenterally for the prevention of influenza and its complications is not threatened by the finding.
2. Is there cause for concern about the use of the new live attenuated vaccine (FluMist), which is given intranasally? This question can only be answered indirectly by the lack of any known relationship between the occurrence of Bell's palsy and influenza epidemics. Moreover, because natural influenza virus infection does not appear to be a precipitating event for the condition, there is no reason to suppose that an attenuated infection induced by a live vaccine such as the intranasal vaccine would confer an increased risk. Thus, there is little reason for concern about the continued use of the new live influenza virus vaccine. However, because the adverse effects of vaccines may not always be immediate, some requiring the passage of time before they are apparent, some degree of surveillance for this complication in recipients of the FluMist vaccine would seem prudent.

Table 10 Asthma-wheezing phenotypes in children

Age of Onset of Wheezing	Transient (<3 yr)	Late-Onset Wheezers (3–6 yr)	Persistent Wheezers (0–6 yr)
Wheezing at 6 yr	0	+	+
Role of maternal smoking	+	0	0
Male predominance	0	+	+
Role of atopy	0	+	+
Elevated serum IgE levels	0	+	+

Source: Ref. 16 (reproduced with permission).

Is There Reason for Concern about the Continued Use of the New Live Influenza Virus Vaccine in Children with Asthma?

Asthma is an immune-mediated inflammatory condition characterized by increased responsiveness to bronchoconstrictive stimuli.²⁴ Although viruses have been shown to play an important role in asthma, with viral infection being responsible for ~85% of exacerbations, the role they play in the development of asthma, however, is more controversial. Some respiratory viral infections, in fact, may be protective and others such as respiratory syncytial virus (RSV) exert a definite pathogenic effect. There is strong evidence for an association between RSV-induced bronchiolitis in infancy and recurrent wheeze up to 12 years of age. Some important population-based studies that followed children from birth or from early childhood into adulthood from the group of Martinez and colleagues^{25,26} have elucidated the patterns of wheezing seen during this period (Table 10 and Fig. 3). Three phenotypes have been identified in children with asthma: (1) transient wheezing, (2) nonatopic wheezing of the toddler and preschool-aged child, and (3) IgE-mediated wheezing. Transient wheezing is associated with symptoms that are limited to the first 3–5 years of life, decreased lung function, maternal smoking during pregnancy, and exposure to other siblings or children at daycare centers. There is no association between transient wheezing and family history of asthma or allergic sensitization. Children wheezing with RSV in the 1st years of life are more likely to be wheezing up to 13 years of age; this is independent of atopy (nonatopic wheezers) and is not related to atopic sensitization. Wheezing associated with evidence of allergic sensitization has been identified as the “classic” asthma phenotype.

Because of this known propensity of respiratory viral infection to be involved in the exacerbation or pathogenesis of asthma, it seems prudent to raise the question of the potential role of FluMist in exacerbating

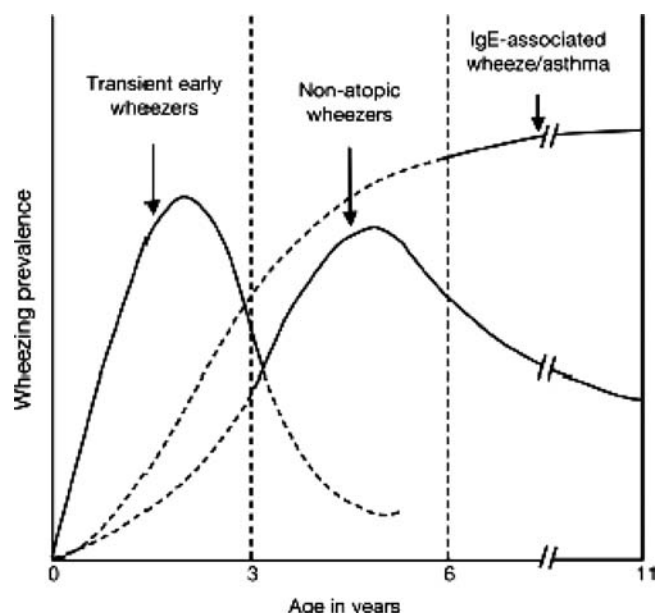


Figure 3. Asthma-wheezing phenotypes in children. (Reproduced with permission from Ref. 25.)

wheezing episodes in a child or adult with asthma or atopy who is a recipient of the vaccine. Bergen *et al.*²⁷ evaluated the safety of CAIV-T vaccine in a large cohort of children and adolescents in a randomized, double-blind, placebo-controlled safety trial in healthy children aged 12 months to 17 years given CAIV (FluMist) or placebo. A significant increased relative risk of reactive airway disease was observed in children 18–35 months of age with a relative risk of 4.06 (90% CI, 1.29–17.86) in this age group. CAIV was generally safe in children and adolescents. At least one event was noted in 14 of 2032 (0.69%) FluMist recipients and 2 of 1025 (0.20%) placebo recipients in this age group. In contrast, another two studies did not find this potential increase in wheezing. In a Wyeth study D153-P514 conducted in 2187 children 6–71 months of age with a history of recurrent respiratory tract infections who received two doses of either CAIV-T or Trivalent Inactivated Vaccine, no statistically significant differences were observed between the two groups for wheezing after dose 1 or dose 2. Similarly, in a second Wyeth study D153-P515, conducted in 2231 children and adolescents 6–17 years of age with asthma who received a single dose of either CAIV-T or Trivalent Inactivated Vaccine, no statistically significant differences between groups were noted for asthma exacerbations (increased asthma medication use, unscheduled clinic visits, or hospitalizations) within the first 42 days or throughout the study surveillance period. Although the safety profile of FluMist has not been definitively established, the observation of a potential increased risk of asthma/reactive airway disease in children <36 months of age is an issue of potential concern and is being examined in larger cohorts of children in this age group.

Table 11 Unresolved issues relating to influenza nasal vaccine

Currently only licensed for 5–49 yr
Groups that need the vaccine the most are <5 yr and >50 yr old
Trials now being conducted in 6- to 59-mon-old children
Question whether the live nasal vaccine can trigger asthma?
Specific issues concerning influenza vaccine availability and usage

Unresolved Issues Relating to the Influenza Nasal Vaccine

Table 11 shows some lingering unresolved issues related to the influenza nasal vaccine. Currently, the vaccine is only licensed for use in individuals who are 5–49 years of age. The groups that need the vaccine the most are <5 years old and >50 years old. Clinical trials are now being conducted in children 6–59 months old and also in older subjects to address the question of whether the vaccine can trigger wheezing in asthmatic or atopic individuals. The most recent issues relate current problems related to vaccine availability and usage. During 2004 a major shortage of influenza vaccine in the United States occurred because of contaminated lots of one of the two major vaccine producers. This has been addressed and should not be a recurring problem. A more serious problem has been the lack of influenza coverage in the older age groups who have asthma, diabetes, and other chronic illnesses.²⁸

A recent publication from the Center for Disease Control and Prevention evaluating influenza and pneumococcal vaccination coverage among adult populations throughout the United States indicates an increase in influenza and pneumococcal vaccination coverage for the majority of areas from 2002 to 2003 among adults aged ≥ 65 years old.²⁸ Median influenza coverage was 69.9% and ranged from 34.9% (U.S. Virgin Islands) to 80.3% (Minnesota). However, for respondents with asthma, median influenza coverage was 34.0% and ranged from 22.5% (Puerto Rico) to 46.6% (Wyoming). Lack of awareness of the need for vaccination was reported common among adults aged <65 years old with high-risk conditions, such as diabetes or asthma.

Because of the 2004 influenza vaccine shortage, vaccine providers have been asked to direct available inactivated influenza vaccine to persons with chronic conditions, such people who have diabetes and/or asthma, and other priority groups. Further analysis of influenza vaccine coverage data will be needed to assess the impact of this shortage on influenza vaccine

coverage and efforts to redirect vaccine to persons at greatest risk for influenza complications. Ensuring adequate amounts of influenza vaccine is critical if vaccination rates of persons at high risk are to continue improving. Pneumococcal vaccine supplies appear to be adequate to meet expected demand. Pneumococcal vaccination should be encouraged for populations at high risk, both to reduce the risk for invasive pneumococcal disease itself and to reduce complications of influenza infection.

REFERENCES

1. Bellanti JA, Zeligs BJ, Mendez de Inocencio J, et al. Alternative routes of immunization for prevention of infectious diseases: A new paradigm for the 21st century. *Allergy Asthma Proc* 22: 173–176, 2001.
2. Sabin AB. Measles, killer of millions in developing countries: Strategy for rapid elimination and continuing control. *Eur J Epidemiol* 7:1–22, 1991.
3. Rapaport HG. Clemens von Pirquet and allergy. *Ann Allergy* 31:467–475, 1973.
4. Bellanti JA, Sabra A, and Zeligs BJ. Gastrointestinal immunopathology and food allergy. *Ann Allergy Asthma Immunol* 93:26–32, 2004.
5. Cutts FT, Clements CJ, and Bennett JV. Alternative routes of measles immunization: A review. *Biologicals* 25:323–338, 1997.
6. Glezen WP. Control of influenza. *Tex Heart Inst J* 31:39–41, 2004.
7. Sabin AB, Flores Arechiga A, Fernandez de Castro J, et al. Successful immunization of children with and without maternal antibody by aerosolized measles vaccine. I. Different results with undiluted human diploid cell and chick embryo fibroblast vaccines. *JAMA* 249:2651–2662, 1983.
8. Sabin AB, Flores Arechiga A, Fernandez de Castro J, et al. Successful immunization of infants with and without maternal antibody by aerosolized measles vaccine. II. Vaccine comparisons and evidence for multiple antibody response. *JAMA* 251: 2363–2371, 1984.
9. Sepulveda-Amor J, Valdespino-Gomez JL, Garcia-Garcia Mde L, et al. A randomized trial demonstrating successful boosting responses following simultaneous aerosols of measles and rubella (MR) vaccines in school age children. *Vaccine* 20:2790–2795, 2002.
10. Bennett JV, Fernandez de Castro J, Valdespino-Gomez JL, et al. Aerosolized measles and measles-rubella vaccines induce better measles antibody booster responses than injected vaccines: Randomized trials in Mexican schoolchildren. *Bull World Health Organ* 80:806–812, 2002.
11. Castro JF, Bennett JV, Rincon HG, et al. Evaluation of immunogenicity and side effects of triple viral vaccine (MMR) in adults, given by two routes: Subcutaneous and respiratory (aerosol). *Vaccine* 23:1079–1084, 2005.
12. Wong-Chew RM, Islas-Romero R, Garcia-Garcia MdeL, et al. Induction of cellular and humoral immunity after aerosol or subcutaneous administration of Edmonston-Zagreb measles vaccine as a primary dose to 12-month-old children. *J Infect Dis* 189:254–257, 2004.
13. Dilraj A, Cutts FT, de Castro JF, et al. Response to different measles vaccine strains given by aerosol and subcutaneous routes to schoolchildren: A randomised trial. *Lancet* 355:798–803, 2000.
14. Dilraj A, Cutts FT, Bennett JV, et al. Persistence of measles antibody two years after revaccination by aerosol or subcutaneous routes. *Pediatr Infect Dis J* 19:1211–1213, 2000.

15. Bellanti JA, Zeligs BJ, Mendez-Inocencio J, et al. Immunologic studies of specific mucosal and systemic immune responses in Mexican school children after booster aerosol or subcutaneous immunization with measles vaccine. [Vaccine 22:1214–1220, 2004.](#)
16. Campion EW. Suspicions about the safety of vaccines. [N Engl J Med 347:1474–1475, 2002.](#)
17. Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. [Lancet 351:637–641, 1998.](#)
18. Madsen KM, Hviid A, Vestergaard M, et al. A population-based study of measles, mumps, and rubella vaccination and autism. [N Engl J Med 347:1477–1482, 2002.](#)
19. Danzig L. Meningococcal vaccines. [Pediatr Infect Dis J 23:285–292, 2004.](#)
20. Rappuoli R. Reverse vaccinology, a genome-based approach to vaccine development. [Vaccine 19:2688–2691, 2001.](#)
21. Rappuoli R, and Covacci A. Reverse vaccinology and genomics. [Science 302:602, 2003.](#)
22. Capecchi B, Serruto D, Adu-Bobie J, et al. The genome revolution in vaccine research. [Curr Issues Mol Biol 6:17–27, 2004.](#)
23. Mutsch M, Zhou W, Rhodes P, et al. Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. [N Engl J Med 350:896–903, 2004.](#)
24. Openshaw PJ, Yamaguchi Y, and Tregoning JS. Childhood infections, the developing immune system, and the origins of asthma. [J Allergy Clin Immunol 114:1275–1277, 2004.](#)
25. Martinez FD. Respiratory syncytial virus bronchiolitis and the pathogenesis of childhood asthma. [Pediatr Infect Dis J 22\(suppl 2\):S76–S82, 2003.](#)
26. Guilbert TW, Morgan WJ, Zeiger RS, et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. [J Allergy Clin Immunol 114:1282–1287, 2004.](#)
27. Bergen R, Black S, Shinefield H, et al. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. [Pediatr Infect Dis J 23:138–144, 2004.](#)
28. Centers for Disease Control and Prevention (CDC). Influenza and pneumococcal vaccination coverage among persons aged > or =65 years and persons aged 18–64 years with diabetes or asthma—United States, 2003. [MMWR Morb Mortal Wkly Rep 53:1007–1012, 2004.](#) □

Property of



OceanSide Publications

IP: 84.221.42.242